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Published in:
Clinical Microbiology and Infection

DOI:
10.1016/j.cmi.2015.05.030

Publication date:
2015

ORIGINAL ARTICLE

Weight-based antibiotic dosing in a real-world European study of complicated skin and soft-tissue infections due to methicillin-resistant *Staphylococcus aureus*

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Abstract

We aimed to characterize real-world dosing of weight-based intravenous (IV) antibiotic therapy in patients hospitalized for methicillin-resistant *Staphylococcus aureus* (MRSA) complicated skin and soft-tissue infections (cSSTIs). This was a subgroup analysis of a retrospective chart review that captured data from 12 European countries. The study included patients ≥18 years old, hospitalized with an MRSA cSSTI between 1 July 2010 and 30 June 2011 and discharged alive by 31 July 2011. Patients treated with IV vancomycin, teicoplanin or daptomycin at any stage during hospitalization were included in this analysis. Analyses were conducted at the regimen level (dosing in mg/kg or in mg, frequency, and total daily dose (TDD)), with potentially multiple regimens per patient, and the patient level, categorizing patients into low, standard (labelled) and high dosing groups according to their initial MRSA-targeted regimen. Among the 1502 patients in the parent study, 998 patients contributed a total of 1050 daptomycin, teicoplanin or vancomycin regimens. Across all regimens, the mean initial TDDs were 6.3 ± 1.9 mg/kg for daptomycin, 10.5 ± 4.9 mg/kg for teicoplanin and 28.5 ± 11.5 mg/kg for vancomycin. A total of 789 patients received first-line therapy with one of the above antibiotics. The majority of patients receiving first-line teicoplanin and daptomycin (96% and 80%, respectively) received higher than labelled cSSTI doses, whereas vancomycin doses were lower than labelled doses in >40% of patients. These real-world data reveal significant deviation from labelled antibiotic dosing in 12 European countries and the potential for suboptimal outcomes in patients with MRSA cSSTIs.

Keywords: Complicated skin and soft-tissue infection, daptomycin, dosing, methicillin-resistant *Staphylococcus aureus*, teicoplanin, vancomycin
Original Submission: 11 November 2014; **Revised Submission:** 13 May 2015; **Accepted:** 14 May 2015
Editor: J.-L. Mainardi
Article published online: 20 July 2015

Presented at: 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Denver, CO, 10–13 September 2013.
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Introduction

Patients with complicated skin and soft tissue infections (cSSTIs) caused by methicillin-resistant *Staphylococcus aureus* (MRSA) commonly receive intravenous (IV) therapy with antibiotics such as vancomycin, teicoplanin or daptomycin [1]. Recommended dosing of these agents is available from a variety of sources, sometimes with conflicting recommendations. For example, recommended doses for IV vancomycin differ

http://dx.doi.org/10.1016/j.cmi.2015.05.030

between the product labelling or licensed dosing (2000 mg/day) [2] and published evidence-based guidelines (30 mg/kg/day) [1,3], with weight-based dosing recommended primarily because of the potential for under-dosing in obese patients with increased volumes of distribution [4,5]. Even when dosing recommendations are consistent, as is the case for daptomycin, doses used in practice frequently differ from those recommended [6].

In order to optimize MRSA antibiotic therapies in patients with MRSA cSSTIs, it is important to accurately characterize the current use of parenteral antibiotic therapy. We therefore performed a subgroup analysis of data obtained from a pan-European retrospective observational medical chart review study to describe real-world, weight-based dosing patterns for daptomycin, teicoplanin and vancomycin therapy in patients hospitalized across 12 European countries for the treatment of MRSA cSSTIs. Additionally, we identified antibiotic dosing patterns according to patient demographics and clinical characteristics, and explored dosing patterns by country.

Methods

This subgroup analysis evaluated data obtained from a retrospective, observational medical chart review study that captured patient information via 342 physicians in 12 European countries [7–9]. Data were obtained from hospital records of patients aged 18 years of age or older hospitalized with a documented MRSA cSSTI between 1 July 2010 and 30 June 2011 and discharged alive by 31 July 2011. Individuals were excluded if they had suspected or proven diabetic foot infection, osteomyelitis, infective endocarditis, meningitis, joint infection, necrotizing fasciitis, gangrene, prosthetic joint infection or prosthetic implant/device infection, significant concomitant infection at other sites (e.g. bacteraemia, pneumonia) or if they had been treated for the same MRSA cSSTI within 3 months of hospitalization. Only patients who used IV vancomycin, teicoplanin or daptomycin at any stage during hospitalization were included within this sub-analysis.

Study investigators randomly selected patients from all the patients in their practice who met the enrolment criteria. Specifically, investigators were instructed to select patients based on randomly assigned birth month and hospitalization month. Data collected included demographic and clinical characteristics, MRSA-targeted IV and oral antibiotic use, and hospital resource use (e.g. length of stay, surgical and diagnostic procedures). The initial MRSA-targeted antibiotic regimen and any subsequent regimens used within the same stay were documented for each patient. Starting and ending doses were collected for each regimen to identify any dose changes that occurred during the course of therapy. Doses that were considered clinically implausible and/or to have been incorrectly transcribed (teicoplanin starting doses $\leq$2 mg/kg/day and any vancomycin dose $\leq$5 mg/kg/day) were excluded from the analysis. Patients were classified according to the initial IV antibiotic used, without regard for drug or dose changes during the course of therapy.

The primary study outcome was the percentage of patients receiving dosing regimens categorized as low, standard, or high (Table 1) based on the total daily dose (TDD) in mg/kg and the labelled or guideline-recommended daily dose at the time the study was conducted [1–3,10,11]. For this analysis, patients were categorized according to the first antibiotic drug prescribed and the dose at the start of therapy, regardless of any subsequent antibiotic switching or dose changes. TDD was calculated for each regimen, both in mg and mg/kg, when data permitted; TDD in mg could not be calculated for patients prescribed a weight-based regimen if their weight was not recorded. The proportion of patients in each dosing category was calculated for each drug, overall and by country. Descriptive statistics were used to summarize patient demographic and clinical characteristics by dosing category. Characteristics that appeared to be distributed differently among groups were further analysed using chi-squared and *t*-tests to identify dosing trends.

Secondary outcomes were analysed at the regimen level, with patients being able to contribute multiple regimens if there were drug or dose changes during the course of treatment. These outcomes included the TDD in mg for each antibiotic at the start and end of therapy, and the distribution of actual

TABLE 1. Daptomycin, teicoplanin and vancomycin labelled doses at study initiation for the treatment of methicillin-resistant *Staphylococcus aureus* complicated skin and soft-tissue infections (cSSTIs) and corresponding dose categories

Drug	Recommended dose(s) for cSSTIs	Dose categories (mg/kg/day)
Daptomycin	4 mg/kg every 24 hours [11]	– Low dose <4.0 – Standard dose 4.0 – High dose >4.0
Teicoplanin	400 mg loading dose (6 mg/kg) followed by 200 mg (3 mg/kg) every 24 h [10]	– Low dose <3.0 – Standard dose 3.0–3.3[a,b] – High dose $\geq$3.4
Vancomycin	2000 mg/day, divided as 1000 mg every 12 h or 500 mg every 6 h [2] 30 mg/kg/day in two divided doses [1,3]	– Low dose <25.0 – Standard dose 25.0–35.0[a] – High dose >35.0

[a]A range of doses was used to define standard dosing to account for dose rounding.
[b]Upper end of dosing range assumes a 6 mg/kg loading dose, followed by 3 mg/kg/day for a total of 10 days.

prescribed regimens (drug, dose and frequency). Other outcomes included the proportion of antibiotic dosing regimens written in mg/kg (weight-based dosing) or mg (flat dosing), and the distribution of regimens by dosing frequency (one to four daily doses).

Results

A total of 1502 patients were included in the parent study. Of these, 977 patients (65%) received first-line therapy with one of the antibiotics of interest; 836 of these patients had sufficient data documented to classify the dosing regimen administered. One patient receiving teicoplanin and 46 patients receiving vancomycin were excluded because of clinically implausible doses, with a total of 789 patients remaining for analysis (Fig. 1). Of note, 43.4% of the patients receiving first-line vancomycin were dosed at <25 mg/kg/day, and first-line teicoplanin regimens were almost all ≥3.4 mg/kg/day (96%). First-line daptomycin doses exceeded 4 mg/kg/day in the majority of patients (80%), and no patients received <4 mg/kg/day. The distribution of category of dosing at start of initial therapy, stratified by country, is shown in Table 2. Countries where >50% of vancomycin starting doses were <25 mg/kg/day were Austria, Czech Republic, Germany, Greece, Portugal and Spain. For daptomycin all starting doses were >4 mg/kg/day in Spain, UK and Slovakia; however, this reflects only one patient in Slovakia. Daptomycin dosing was in accordance with the labelled dose for MRSA cSSTI (4 mg/kg/day) >50% of the time in Austria; in all other countries, dosing was predominantly >4 mg/kg. No patients received daptomycin as the initial therapy for MRSA cSSTIs in Czech Republic, Ireland, Portugal or Poland.

Demographic and clinical characteristics of study patients by drug and dosing category are shown in Table 3. Among patients for whom height and weight data were recorded, obesity was over twice as common among patients receiving vancomycin doses of <25 mg/kg/day (69.9%) than in patients receiving higher doses (33.0% and 27.3% in the standard and high-dose groups, respectively; $p < 0.001$). The prevalence of moderate to severe renal dysfunction (as defined and documented in the medical record) was higher in patients receiving a vancomycin daily dose of <25 mg/kg (18.8%) than in those receiving a daily dose of ≥25 mg/kg (8.8%; $p < 0.001$). Further exploration of vancomycin dosing revealed that the mean TDD at the start of therapy was lower in patients with moderate to severe renal insufficiency (1556 mg) compared with those without renal insufficiency (2017 mg; $p < 0.001$). Because of the small numbers of patients in several of the teicoplanin and daptomycin dosing categories, no conclusions regarding dosing trends can be drawn.

For the antibiotic dosing regimen-level analyses, a total of 945 patients (63%) contributed a total of 997 antibiotic

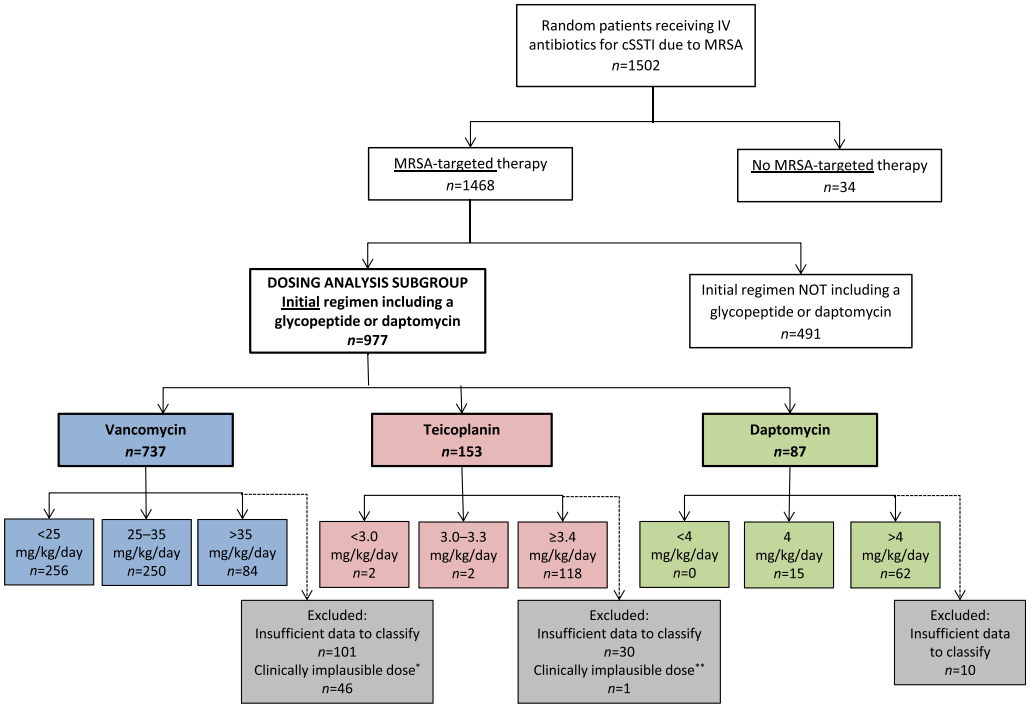

FIG. 1. Analysis of methicillin-resistant *Staphylococcus aureus* (MRSA) complicated skin and soft-tissue infection (cSSTI) antibiotic treatment patterns. *Defined as any vancomycin dose ≤5 mg/kg/day; **defined as a teicoplanin starting dose ≤2 mg/kg/day; IV, intravenous.

TABLE 2. Vancomycin and daptomycin total daily dose (in mg/kg/day) at start of therapy by country (initial regimen)[a]

	Vancomycin				Daptomycin			
Country	**Total** ***n***	**<25**	**25–35**	**>35**	**Total** ***n***	**<4**	**4**	**>4**
Austria	12	66.7%	16.7%	16.7%	6	0%	66.7%	33.3%
Czech Republic	17	58.8%	29.4%	11.8%	0	N/A[b]	N/A[b]	N/A[b]
France	144	16.0%	66.0%	18.0%	3	0%	33.3%	66.7%
Germany	107	66.4%	29.0%	4.6%	9	0%	22.2%	77.8%
Greece	18	61.1%	22.2%	16.7%	17	0%	11.8%	88.2%
Ireland	1	0%	0%	100%	0	N/A[b]	N/A[b]	N/A[b]
Italy	74	25.7%	56.8%	17.5%	20	0%	30.0%	70.0%
Poland	15	46.7%	40.0%	13.3%	0	N/A[b]	N/A[b]	N/A[b]
Portugal	71	63.4%	25.4%	11.3%	0	N/A[b]	N/A[b]	N/A[b]
Slovakia	11	36.4%	27.3%	36.4%	1	0%	0%	100.0%
Spain	68	54.4%	38.2%	7.4%	12	0%	0%	100.0%
United Kingdom	52	40.4%	34.6%	25.0%	9	0%	0%	100.0%
All countries	590	43.4%	42.4%	14.2%	77	1.0%	19.4%	79.6%

[a]Excludes patients for whom total daily dose could not be calculated due to weight not being recorded.

[b]No patients received initial therapy with daptomycin in Czech Republic, Ireland, Poland or Portugal.

Colour coding as follows: <20%, 20–50%, >50%, N/A: no available patients.

Due to rounding, percentages may not sum to 100%.

regimens that included daptomycin (*n* = 110), teicoplanin (*n* = 178) or vancomycin (*n* = 709). There was significant variability in the dosing regimens prescribed for all three drugs. The most frequently prescribed regimen for each drug was administered to approximately 25% of patients (Table 4). The mean initial TDDs were 6.3 ± 1.9 mg/kg for daptomycin, 10.5 ± 4.9 mg/kg for teicoplanin and 28.5 ± 11.5 mg/kg for vancomycin. Mean and median TDD for daptomycin- and vancomycin-treated patients were similar at the start and end of therapy, whereas the mean and median TDD for teicoplanin were higher at the start compared to the end of therapy, reflecting loading dose administration (Table 5).

A flat or mg dosing regimen was prescribed for the majority of teicoplanin (89%) and vancomycin (76%) regimens, whereas weight-based dosing was used most frequently for daptomycin (59%). At the start of therapy, vancomycin was most often dosed twice daily (56%), followed by once daily (22%), four times daily (15%) and three times daily (7%). Teicoplanin starting doses were equally divided between twice daily (50%) and once daily (48%), with a few regimens dosed three times daily (2%). Daptomycin was dosed once daily almost universally (98%), with the remaining regimens dosed three times daily (2%).

A *post hoc* analysis was conducted to describe the dosing of teicoplanin using the updated labelled dose approved in

TABLE 3. Patient characteristics by initial methicillin-resistant *Staphylococcus aureus*-targeted regimen

	Total daily dose, mg/kg							
	Vancomycin (*n* = 590)			Teicoplanin (*n* = 122)			Daptomycin (*n* = 87)	
	<25	25–35	>35	<3.0	3.0–3.3	≥3.4	4.0	>4.0
Patients, *n* (%)	256 (43.4)	250 (42.4)	84 (14.2)	2 (1.8)	2 (1.8)	11 (96.4)	15 (17.2)	62 (71.3)
Male, %	60.6	65.6	53.6	0	50.0	61.0	66.7	62.9
Age, years[a]	62.7 ± 14.9	59.0 ± 16.1	52.3 ± 16.7	64.0 ± 8.5	49.5 ± 19.1	62.3 ± 16.4	60.6 ± 11.9	55.0 ± 17.3
Weight, kg (*n*)[a,b]	82.1 ± 13.4 (245)	73.4 ± 11.7 (243)	67.0 ± 13.4 (80)	74.5 ± 4.9 (2)	69.0 ± 12.7 (2)	76.3 ± 16.9 (118)	75.7 ± 9.7 (13)	76.8 ± 13.6 (55)
Obese, % (*n*)[b,c]	69.9% (226)	33.0% (212)	27.3% (66)	50.0% (2)	100% (1)	44.9% (98)	38.5% (13)	48.8% (43)
Comorbidities, %								
Diabetes	37.5	27.6	29.8	50.0	0	31.4	40.0	11.3
Peripheral vascular disease	31.6	17.6	21.4	100	0	17.0	33.3	22.6
Chronic pulmonary disease	20.7	23.2	8.3	33.3	100	22.9	20.0	19.4
Coronary artery disease	27.3	14.4	8.3	0	50	12.7	13.3	19.4
Congestive heart failure	28.9	12.0	6.0	0	0	12.7	26.7	14.5
Moderate to severe renal disease	18.8	8.8	6.0	100	0	5.1	0	9.7
Cerebrovascular disease	12.9	7.6	10.7	0	0	11.9	0	6.5
Mild liver disease	13.7	9.2	8.3	0	0	10.2	0	12.9
Peptic ulcer disease	9.0	8.8	8.3	0	50	7.6	6.7	16.1
Dementia	8.2	5.2	3.6	0	0	6.8	6.7	3.2
Complicated skin and skin structure infection type, %								
Deep/extensive cellulitis	25.8	23.6	25.0	0	0	22.0	20.0	35.5
Infected ulcer	26.2	22.4	15.5	100	0	28.8	26.7	14.5
Major abscess	15.6	22.4	21.4	0	0	18.6	13.3	19.4
Post-traumatic wound infection	16.0	15.6	14.3	0	100	12.7	13.3	12.9
Surgical site infection	10.6	11.6	17.9	0	0	12.7	20.0	9.7
Infected burn	6.9	3.2	6.0	0	0	3.4	6.7	6.5
Other	0	1.2	0	0	0	1.7	0	1.6
Sepsis, %	24.6	19.6	19.1	0	0	13.6	26.7	16.1

[a]Mean ± SD.
[b]Number of patients with data available.
[c]Obese defined as >120% of ideal body weight; could not be determined for patients with weight and/or height data not recorded.

2013 [12]. A daily dose of <6 mg/kg was classified as low dose, 6–6.6 mg/kg as standard dose, and >6.6 mg/kg as high dose. This analysis found that the majority of teicoplanin starting doses (70%) were still in the high-dose category. Approximately 5% of teicoplanin doses were classified as standard dose and 25% of doses were classified as low dose.

TABLE 4. Daptomycin, teicoplanin and vancomycin regimens prescribed for >5% of patients (any stage or regimen)

Drug	Regimen	*n* (%)
Daptomycin (*n* = 110)	6 mg/kg daily	27 (24.5)
	500 mg daily	23 (20.9)
	4 mg/kg daily	19 (17.3)
	8 mg/kg daily	12 (10.9)
	350 mg daily	8 (7.3)
	700 mg daily	7 (6.4)
	Other	14 (12.7)
Teicoplanin (*n* = 178)	400 mg daily	42 (23.6)
	400 mg twice daily	42 (23.6)
	800 mg daily	21 (11.8)
	200 mg twice daily	15 (8.4)
	600 mg twice daily	14 (7.9)
	Other	44 (24.7)
Vancomycin (*n* = 709)	1000 mg twice daily	203 (28.6)
	500 mg four times daily	90 (12.7)
	500 mg twice daily	72 (10.1)
	1000 mg daily	55 (7.8)
	15 mg/kg twice daily	48 (6.8)
	30 mg/kg daily	46 (6.5)
	Other	195 (27.5)

Discussion

Results from this analysis of real-world IV antibiotic use for the treatment of hospitalized patients with MRSA cSSTIs show considerable variation in antibiotic dosing practices among the 12 European countries outlined. This variability may result from country-specific practice patterns, and possible differences in the disciplines involved in antibiotic prescribing (e.g. infectious disease specialists, antibiotic stewardship teams, pharmacists) across countries. Doses were prescribed in mg for the majority of teicoplanin or vancomycin regimens, whereas weight-based dosing (i.e. mg/kg) was prescribed for the majority of daptomycin regimens. The initial dosing frequency prescribed most commonly for vancomycin regimens was twice daily and for daptomycin regimens was once daily. Teicoplanin regimens were almost equally split between once and twice daily. In general, there was significant variability in the dosing regimens prescribed for all three drugs.

The most common vancomycin dosage regimen in this study was 1000 mg IV twice daily. Analysis of initial MRSA-targeted regimens by weight showed that over 40% of the patients receiving vancomycin for an MRSA cSSTI received a daily dose <25 mg/kg. This dose is less than the recommended daily dose of 30–60 mg/kg for patients with normal renal function [3,13].

TABLE 5. Daptomycin, teicoplanin and vancomycin mean and median initial and final total daily dose (any stage of regimen)

	Vancomycin	Teicoplanin	Daptomycin
Patients, *n*/*N*[a]	683/709	177/178	96/110
Mean daily dose ± SD, mg			
Start of therapy	1915.4 ± 788.0	707.2 ± 339.2	486.9 ± 147.2
End of therapy	1848.2 ± 798.8	514.1 ± 299.5	477.4 ± 144.2
Median daily dose (range), mg			
Start of therapy	2000 (500–7080)	800 (180–1872)	500 (240–1080)
End of therapy	2000 (500–7080)	400 (100–2000)	500 (240–1080)

[a]*n*, number of patients for whom the total daily dose could be calculated (patient weight available); *N*, total number of patients receiving drug.

Administration of low vancomycin doses may not only decrease vancomycin effectiveness but also increase the development of vancomycin intermediate susceptible and/or vancomycin-resistant *S. aureus* strains [13]. However, as this study did not collect vancomycin serum levels or institution-specific MICs, we could not evaluate the potential for development of resistant organisms at the various institutions.

Analysis of patient-level data found an increasing prevalence of renal dysfunction and obesity with decreasing vancomycin dose. As expected, analysis of vancomycin dosing based on patient renal status found that patients with moderate to severe renal insufficiency, compared with those without, received lower vancomycin daily dose. However, as vancomycin levels and local reference ranges were not collected, we were unable to determine whether vancomycin was appropriately dosed according to renal function. With regard to obesity, current recommendations are to dose vancomycin based on a patient's actual body weight, not ideal body weight [13]. Use of ideal body weight would result in a lower mg/kg dose for obese patients and could negatively affect patient outcome. In this study, we found that almost 70% of patients receiving a vancomycin daily dose of <25 mg/kg were obese.

Comparison of the average starting and ending teicoplanin doses suggests the use of a teicoplanin loading dose for some patients, although we do not have the data needed to confirm that this is indeed the case. Although the labelled dosing of teicoplanin at study initiation consisted of a 6-mg/kg loading dose on day 1 followed by a 3-mg/kg daily maintenance dose [10], >50% of teicoplanin starting regimens were dosed more frequently than once daily at treatment initiation. Analysis of the ending teicoplanin dose suggests use of a higher than recommended teicoplanin maintenance dose (mean daily dose of 510 mg).

These higher teicoplanin doses may reflect data supporting the teicoplanin label change made in late 2013. In October 2013, the teicoplanin label was revised and a new dose for treating MRSA cSSTIs was included. The new recommended teicoplanin dose for patients with MRSA cSSTIs is 400 mg (~6 mg/kg) every 12 h for three doses followed by a daily dose of 6 mg/kg [12]. However, it should be noted that this change was some time after the patients included within this study were treated. In addition, a targeted trough concentration of >15 mg/L by fluorescence polarization immunoassay is recommended in the product labelling. There is other evidence to suggest that even higher than recommended teicoplanin doses are needed to achieve therapeutic drug levels of 20–60 mg/L [14]; however, because our study did not collect teicoplanin serum levels, we could not evaluate the adequacy of dosing according to the recommended range.

The majority of patients (80%) prescribed first-line daptomycin in this study received a dose that exceeded the approved and recommended 4 mg/kg daily dose for the treatment of MRSA cSSTIs [1,3,11]. In four of the 12 study countries (Portugal, Slovakia, Spain, UK), high doses were used exclusively. Although it is possible that some of the high doses of daptomycin can be explained by dose rounding, analysis by dosing regimen found that the most common daptomycin regimen used in this study was daptomycin 6 mg/kg/day, the recommended daily dose for the treatment of bacteraemia [11]; however, patients with bacteraemia were excluded from this study. These results are consistent with data from the last analysis of the European registry for the Cubicin® Outcomes Registry and Experience (EU-CORE), which showed that 43% of patients treated for cSSTIs received a daptomycin daily dose of 6 mg/kg or more [6]. Use of higher than approved and recommended daptomycin doses for the treatment of cSSTIs has not only economic but also clinical implications. Whereas patients receiving a dose of 6 mg/kg/day had elevations in creatine phosphokinase more frequently than patients receiving comparator regimens (6.7% versus 0.9%; p 0.004), doses of 4 mg/kg/day were not significantly associated with creatine phosphokinase elevations (2.1% versus 1.4% for comparator regimens) [15,16].

Several limitations of the study reflect the observational design of the parent study and the *post hoc* nature of the analysis. Data collected on antibiotic dosing were limited to starting and ending regimens, and so any other dose changes were not captured. We were unable to make associations between antibiotic dosing and clinical outcomes because treatment success rates were collected only at discharge, with >99% of patients exhibiting cure or improvement, regardless of the antibiotic prescribed.

In conclusion, results from this real-world analysis of parenteral antibiotic treatment patterns in patients with MRSA cSSTIs hospitalized in Europe show wide variability in dosing regimens for patients with MRSA cSSTIs, particularly the frequent use of higher than labelled doses for teicoplanin and daptomycin, and the issue of potential under-dosing of vancomycin in obese patients. These data reveal significant variation

in clinical practice and the potential for suboptimal clinical and economic outcomes. Clinicians with patients with MRSA cSSTIs under their care should be cognisant of the recommended dosing of MRSA-active antibiotics in order to maximize clinical benefit to patients while avoiding unnecessary antibiotic use.

Transparency declaration

W. Lawson has received travel support for attending meetings and fees for advisory boards from Astellas and Pfizer. D. Nathwani has received lecture fees, travel support for attending meetings and fees for advisory boards from Astellas, Astra-Zeneca, Bayer, Cubist, Durata, Medicines Company, Biomerieux & Pfizer Inc. He has received no fees in relation to this manuscript. C. Eckmann has received lecture fees, travel support for attending meetings and fees for advisory boards from Bayer, AstraZeneca, Cubist, Durata and Pfizer. S. Corman, J. Stephens and C. Solem are employees of Pharmerit International, who were paid consultants to Pfizer in connection with this study. C. Macahilig is an employee of Medical Data Analytics, a subcontractor to Pharmerit for this project. J. Li, C. Charbonneau, N. Baillon-Plot and S. Haider are employees of Pfizer.

Acknowledgement

The authors wish to thank Beth Lesher, PharmD, BCPS for medical writing support.

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